Expert Opinion

Practical approaches of taste masking technologies in oral solid forms

Dionysios Douroumis
Phoqus Pharmaceutical Limited, 10 Kings Hill Avenue, Kings Hill, West Malling, ME19 4PQ, Kent, UK

In the pharmaceutical industry, taste masking techniques are applied to prevent active pharmaceutical ingredients exhibiting a bitter and unpleasant taste. The oral administration of bitter drugs through solid dosage forms requires an acceptable degree of palatability, patient tolerance and significant therapeutic value. In the recent years, enormous progress in taste masking technologies has given rise to novel strategies such as fast dissolving dosage forms, chewable tablets and coating of molten materials. Similarly, common technologies applying double coating layers, microencapsulation or even chemical modification have been employed to improve patient compliance. This review endeavours to present the practical technologies and platforms applied for taste masking and indicate the most interesting features of each approach.

Keywords: fast dissolving tablets, inclusion complexation, microencapsulation, solid dispersions, taste masking

Expert Opin. Drug Deliv. (2007) 4(4):417-426

1. Introduction

Taste masking is of critical importance for active ingredients with an unpleasant bitter taste, due to the need for increased patient compliance. In the pharmaceutical industry, taste masking technology involves the development of a system that prevents the active substance interacting with the taste buds, thereby eliminating or reducing the negative sensory response.

Recent developments in taste masking technology have presented viable and robust dosage platforms with excellent taste masking properties. Therefore, the scope of this review is to identify common and novel taste masking technologies of oral solid forms presently employed in the pharmaceutical industry. This does not include taste masking formulation options such as the incorporation of flavours and sweeteners. Most of these technologies enable excellent taste and odour masking, reduced drug dosage, enhanced therapeutic effect, improved drug adsorption rates and patient compliance.

There are three general taste masking principles (**Figure 1**): the use of a physical barrier, chemical or solubility modification, and solid dispersions, each of them further subdivided into several methods. Additionally, unique platforms such as orally disintegrating and chewable tablets, applicable for taste masking have been extensively employed. This review focuses on the present status, trends and the commercial applicability of existing technologies.

2. Fast dissolving platforms

Fast dissolving dosage forms (FDDFs; **Table 1**), also known as orally disintegrating tablets (ODTs), are a recent and viable technological development for bitter

10.1517/17425247.4.4.417 © 2007 Informa UK Ltd ISSN 1742-5247

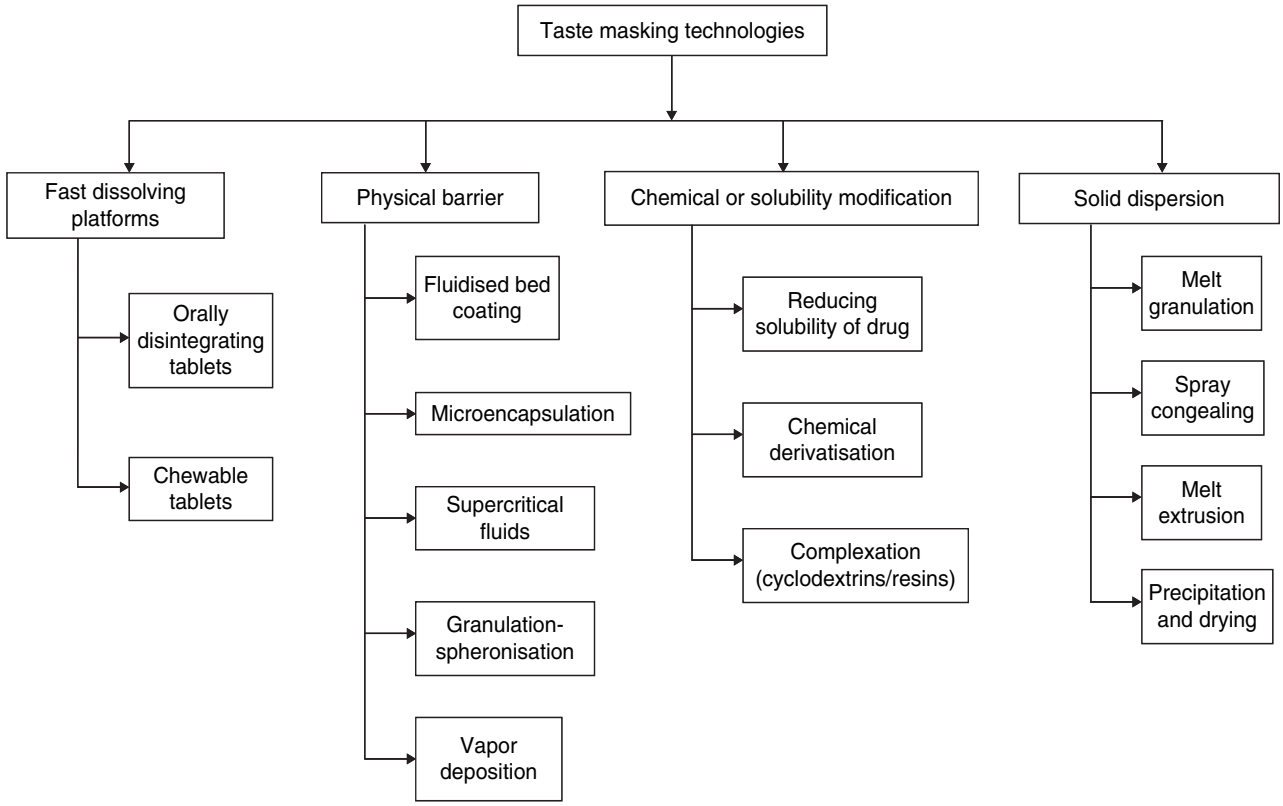

Figure 1. General taste masking principles.

taste masking. ODTs that disintegrate and/or dissolve rapidly in the saliva without the need for water appear advantageous to conventional tablet forms. ODTs, as novel dosage forms, have several characteristics to distinguish them from the more traditional ones. The major advantage of ODT formulations is that they combine the advantages of both liquid and conventional tablet formulations [1]. They provide the convenience of a tablet, while also allowing the ease of swallowing provided by a liquid. Furthermore, the administration of ODTs is easier for children and the elderly as they do not have to swallow the medication with water. Taste masking is of critical importance in the formulation of an acceptable ODT. Present methods of taste masking in fast dissolving/disintegrating tablets in some cases include sweeteners and flavourings. However, these are not a sufficient means for taste masking a number of bitter drugs. Another major challenge is subjecting coated drug particles to the compaction process. In many instances, during tabletting of standard tablet formulations, the coating fractures, causing premature release of the drug into the mouth. When coated particles are needed to mask the bitter and unpleasant taste of a drug in an ODT, the low compaction force of ODT technology is advantageous, as it reduces the probability of the barrier coating fracturing during the compression process.

Most ODT technologies incorporate unique taste masking forms, rendering them expedient. The primary methods of taste masking include adsorption onto or complexation with carriers and spray coating of drug particles. Moreover, ODTs implement novel technologies such as freeze drying, spray drying, molding, spinning, effervescence, sublimation, sintering, the addition of specific excipients (calcium salt, sugars, disintegrants) and the common compression processes. The integration of various methods depends on the drug's physicochemical properties. In brief, some of the FDDF technologies are now described.

Zydis® (Cardinal Health), a FDDF tablet [2,101-103], is produced by lyophilising or freeze drying the drug in a matrix usually consisting of gelatin, flavours and sweeteners to optimise the taste of the dosage form. The solvent is removed from a frozen drug solution or a frozen drug suspension containing structure-forming excipients. It dissolves on the tongue in 2 – 3 s [3]. In addition, it uses microencapsulation with specialised polymers or complexation with ion exchange resins to mask the bitter-tasting drug. The combination of lyophilisation and taste masking creates a product that is satisfying to the senses of taste and touch. However, the process of freeze drying is a relatively expensive manufacturing process. The Zydis formulation is also very lightweight and fragile, and it has poor stability at higher temperatures and humidity. It readily absorbs water, and is very sensitive to degradation at relative humidity > 65%. Presently there are several commercial drug formulations combined with Zydis,

Table 1. Commercial fast dissolving dosage forms products.

Product FDDF	Active agent	Indications	Company – Partner
Alavert™	Loratadine Pseudoephedrine sulfate	Antihistamine nasal decongestant	CIMA – Wyeth Consumer Health
Benadryl® Fastmelt™	Diphenhydramine citrate	Antihistamine	Yamanouchi – Pfizer
Claritin® RediTabs®	Loratadine	Antihistamine	R.P. Scherer – Schering-Plough
Dimetapp®	Loratadine	Antihistamine	Wyeth
Excedrin® QuickTabs™	Acetaminophen caffeine	Pain reliever	Ethypharm – BMS
Maxalt® MLT	Rizatriptan benzoate	Migraine	R.P. Scherer – Merck
NuLev™	Hyoscyamine sulfate	Irritable bowel syndrome	CIMA – Schwarz Pharma
Pepcid RPD®	Famotidine	Heartburn	Johnson & Johnson – Merck Pharmaceuticals Co.
Remeron® SolTabs™	Mirtazapine	Depression	CIMA – Organon
Tempra® FirsTabs	Acetaminophen	Pediatric analgesics	CIMA – Bristol-Myers Squibb
Triaminic® SoftChews®	Pseudoephedrine, acetaminophen, dextromethorphan	Throat pain and cough	CIMA – Novartis Consumer Health
Tylenol®	Acetaminophen	Headache	McNeil PPC
Zofran®	Ondansetron HCl	Nausea and vomiting	R.P. Scherer – Glaxo SmithKline
Zomig® ZMT and Rapimelt	Zolmitriptan	Migraine	CIMA – Astra Zeneca
Zyprexa® Zydis®	Olanzapine	Schizophrenia	R.P. Scherer – Eli Lilly

FFDF: Fast dissolving dosage forms products.

such as loratadine, piroxicam, rizatriptan, famotidine, olanzapine and ondansetron.

OraSolv® (Cima Labs) [104-106] is also a fast-dissolving/disintegrating dosage form. The OraSolv technology disperses in the saliva with the aid of almost unnoticeable effervescence. The tablet matrix dissolves in less than 1 min, leaving coated drug powder. The taste masking strategy in the OraSolv formulation is twofold: the unpleasant flavour of the drug is not only neutralised by sweeteners or flavours, but both drug powder coating and effervescence are used in this technology. The drug substance incorporated in the tablet is in microparticulate form. Thus, the microparticle matrix covers the bad taste and controls the release profile. The major disadvantage of the OraSolv formulation is its mechanical strength. The OraSolv tablet has the appearance of a traditional compressed tablet. However, the tablets are compressed with very low tensile strength, yielding a weaker and more brittle tablet in comparison with conventional ones. Formulations of mirtazepine and acetaminophen are on the market.

DuraSolv® (Cima Labs) is [107,108] a second-generation fast-dissolving/disintegrating tablet formulation. It is produced in a mode similar to OraSolv, but offers much higher mechanical strength due to the use of higher compaction pressures during tabletting. Due to a non-direct compression filler, which represents the main ingredient and offers substantial tensile properties, the DuraSolv matrix is produced in a faster, more cost-effective manner and it can be packaged in either traditional blister packaging or vials. However, due to high compaction pressure, the drug powder may become fractured, especially for high drug-loading doses and, thus, expose the bitter taste.

The use of lipids [109] in ODTs has also been proven successful in masking bitter active agents. A large range of suitable lipids, such as lecithins, phospholipids, glycolipids and non-saturated fatty acids, can be combined with a water-soluble polymeric carrier into a solution or suspension. Furthermore, the suspension is dosed into blister packets, frozen and freeze dried to produce the final taste-masked formulation. The association between the pharmaceutically active substance and the lipid may either be through partitioning into the lipid structures, by direct binding of the pharmaceutically active substance to the lipid molecules, or by adsorption of the pharmaceutically active substance onto the surface of the insoluble lipid particles.

There are also several FDDF formulations to mask the taste of bitter drugs, for example FlashTab® (Ethypharm) [110,111] Ceform™ (Biovail) [4] and Oraquick® (KV Pharmaceuticals) [5], and EasyTec™ (Antares Pharma) [112].

A novel formulation offering unique taste-masking possibilities is the Medichew® (Fertin Pharma) gum [6,7,113] technology. A piece of chewing gum usually consists of a gum core, which may or may not be coated. The core is composed of an insoluble gum base (resins, elastomers, emulsifiers, fillers, waxes, antioxidants and softeners), sweeteners, flavouring

agents and active substances. As many active substances are bitter, a common method to mask taste is the encapsulation or complexation of the active pharmaceutical ingredient by incorporating cyclodextrins or resins. The development of such products includes the adjustment of sweetener level and release, depending on the active properties and release profile of the product. In short, the manufacturing process comprises the mixing of a gum base, a taste-masked active ingredient and sweeteners.

Another approach is the use of EnVel® technology (Cardinal Health) [201] to surround the bitter active pharmaceutical ingredient with pharmaceutically acceptable excipients. The EnVel Technology provides a simple and easy method of manufacturing chewable tablets that contain a pharmaceutical active agent requiring taste masking. It uses a standard mixture of excipients that are processed using common wet granulation and spheronisation techniques. The active ingredient is enveloped as a matrix using excipients or the active agent is isolated as discrete particles using a hydrocolloid polymer (microcrystalline cellulose and methylcellulose). The resultant particles are taste masked. Due to the manufacturing method, additional flavours can be added to the fine particles to further optimise the taste masking of the active pharmaceutical ingredient.

3. Application of physical barrier

The most common method to taste mask a bitter or unpleasant drug is the use of physical barriers or coating. A physical barrier coated onto the active ingredient could successfully provide a palatable oral dosage form, as the coating prevents early dissolution of drug in the mouth. However, as the tablet matrix dissolves away, the masked drug particles can be left in the mouth with a gritty and sandy texture, due to the large particle size and the insoluble membrane of the coated particles. This also raises some concern with conventional tablet dosage forms, as any negative effect on palatability is not desirable. The primary aim is to formulate an oral dosage form that effectively masks both the texture and taste of the active material.

Fluidised bed coating technology is a commonly used approach to apply a continuous coat around the core particle. Generally there are two types of techniques that can be applied when using fluidised bed coating technology: coating using a polymeric solution [114-116] or using molten materials [117,118]. The conventional coating process is widely used but involves solvent solutions that must be evaporated, and the coating materials are applied as solutions or dispersions (30% solid material). However, this method offers a wide range of suitable polymers that are appropriate for the taste masking of highly bitter and unpleasant tasting drugs, and it prevents the grittiness of coated particles. The amount of the coating polymer in the active granules varies 10 – 40%, depending on the granule properties and the bitterness of the drug.

Using the fluidised bed coating process, dextromethorphan hydrobromide and chlorphenamine maleate [114] have been efficiently masked. Prior to coating, the active agents were granulated with mannitol and polyvinylpyrrolidone (PVP K30). The coating solution consisted of ethylcellulose, PVP and acetylated monoglycerides. The application of a double coating layer is also a well-established practice. In this way, drug granules have also been coated with a double polymeric layer to eliminate the bitterness of cetirizine HCl [115]. The inner coating layer is composed of a saliva-insoluble polymer, such as Eudragit RS30, and the outer layer of a water-permeable polymer (Eudragit RL30D). Similarly, a rapidly releasing and taste-masking pharmaceutical dosage form [116] has been developed consisting of a core containing sildenafil citrate, low-substituted hydroxypropyl cellulose and microcrystalline cellulose. The inner coating layer, formed over the core, contains a water-soluble polymer such as hydroxypropyl methylcellulose; the outer coating layer, formed over the inner coat, contains a saliva-insoluble polymer (cellulose or methacrylate grades).

An alternative approach is the selection of a material that can be applied in a molten state. The GatteCoat™ (Gattefossé) technology [117] involves spraying a melted lipidic ester on powders or granules, and is a solvent-free process. A lipid layer of ~ 10 µm is formed around the particles, and the active agent comprises 95% of the finished product. The lipids used in this technology are naturally derived mixed glycerides. A similar approach [118] involves meltable wax materials composed of a mixture of hydrophobic material (e.g., glyceryl monostearate) and an oil-absorbing polymeric compound. In these cases, coating can be applied to pure crystalline active ingredients or granules (a mixture of active ingredient with other excipients such as binders). The materials are suitable for water-soluble or water-insoluble highly bitter drugs, and when the active agent is combined in tablet form, the dissolution characteristics are affected significantly.

Furthermore, spray drying has been applied as an alternative way to provide a physical barrier. A micromatrix active powder [119] has been produced by mixing nizatidine with a cationic polymer (Eudragit E100) dissolved in an organic solvent; the solution is then spray dried. The obtained micromatrix powder has presented acceptable palatability with 1:6 drug–polymer ratios. The main disadvantage of spray drying is the use of organic solvents in many cases and the increased polymer quantities. The latter can result in retarded drug release profiles depending on the porosity of the obtained powder. The relative high nozzle temperatures make spray drying inappropriate for heat-sensitive active agents.

Among the physical barrier technologies, microencapsulation of bitter drugs is an extensively applied process that is used in a number of commercial products. In order to achieve more pleasant dosage forms, microencapsulation techniques with various polymers have been developed and described in the literature [8-14]. For example, Microcaps® (Eurand) is a well-recognised technology used to encapsulate drug substances [120-122]. It is a flexible and precise technique

that provides uniform coated drug particles. By applying coacervation/phase separation processes, it is possible to use different polymeric membranes with various porosity properties. Thus, the release rate profiles, organoleptic features and drug dosage can be determined through the type and the level of the selected polymer. To achieve a superior taste, the Microcaps coacervation process creates a physical barrier between the bitter active pharmaceutical ingredient and the taste buds using ethylcellulose as the encapsulating polymer to place a uniform coating of polymeric membrane of varying thicknesses and porosities directly onto crystals or granules. Furthermore, Microcaps can be combined with AdvaTab® (Eurand) ODT technology, to produce taste-masked ODTs with excellent physical robustness, mouth feel and disintegration properties. In general, microencapsulation techniques offer great advantages, such as effective and consistent coating, a wide range of particle sizes, increased drug stability and the ability to coat drug crystals or granules. The produced microcapsules are blended with other excipients and compressed into tablets. In order to prevent microparticles fracturing, either flexible polymers are used or low compression forces are applied during manufacture. Various polymers such as gelatin, povidone, hydroxyethyl cellulose, ethyl cellulose, bees wax, carnuba wax and shellac are used as candidate coating agents.

A rather limited approach for taste masking is the use of supercritical fluids (SCFs) [123,124], which is a one-step process. SCFs offers considerably promise for taste masking through the formation of microparticles. The solvating power of SCFs makes it possible to separate a particular component from a multicomponent mixture. Among the major advantages of SCFs is the high degree of control over physicochemical properties (particle size, morphology), product homogeneity, and the single-step production. In some cases, a metastable amorphous drug form is produced to increase solubility and bioavailability compared with the crystalline form. Carbon dioxide is one of the most commonly used supercritical solvents because of its relatively low critical temperature and pressure (critical temparature = 31.1°C, critical pressure = 73.8 bar). The low critical temperature of carbon dioxide makes it attractive for processing heat-sensitive active ingredients. Typically, the drug and the polymers are dissolved in an organic solvent and then sprayed into a high-pressure chamber filled with supercritical carbon dioxide. SCF technology has been successfully applied to provide a fluffy, taste-masked aspartame powder [123]; the powder consists of needle-shaped microcrystals covered by ethyl cellulose. Nevertheless, SCFs are not widely applicable because of their expensive costs, limited polymer/drug solubility in carbon dioxide and insufficient drug loading in some cases.

An alternative coating method is to use a vapour deposition process [125,126] to coat drug with polymers such as poly-p-xylylene (Parylene C). Parylene C is not considered as a toxic material (class VI plastic), as it has been subjected to and has passed a variety of biological evaluations by the FDA. In this method, Parylene C is vaporised at a temperature > 170 °C, followed by pyrolysis of the vapours at ~ 690 °C to form the gaseous reactive monomer para-xylxylene. This reactive monomer is deposited onto the drug particle. The drug particle, which has a lower temperature, causes the reactive monomer to condense on the surface of the drug particle and polymerise. Sample dissolution results of this microencapsulated drug (theophylline) showed that a slow release profile is obtained compared with the uncoated particle. Furthermore, the major disadvantage of this novel technique is the requirement of drugs with a relatively high melting point.

4. Solubility modification

Solubility modification is used to reduce the solubility of a drug in the mouth and, therefore, the bitterness exhibited by the drug. For example, the solubility of sildenafil citrate [127] is reduced by incorporating sodium carbonate into the FDDF tablet. As the solubility of sildenafil is dependent on the pH, with maximal solubility at pH 2.0, incorporation of sodium carbonate as an alkalising agent reduces the solubility of sildenafil citrate in the mouth. Although solubility modification is a simple process, it is applicable only to those drugs that have a pH-dependent solubility. Thus, the applicability of this technique to variety of drugs is limited.

An alternative method used to reduce drug bitterness is wet granulation of the active agent with water-insoluble materials. The concepts of wet granulating and the granulations prepared by such a process are well known. In a wet-granulation process, the material to be granulated, usually in powdered form, is wetted with an aqueous composition of a granulating agent to cause the powdered material to agglomerate. This agglomerated product is subsequently dried and then generally milled to reduce the size of the agglomerates to that suitable for use.

Ibuprofen has been efficiently masked using hydroxypropyl methylcellulose phthalate (HPMCP) [128]. As HPMCP is not soluble in pure water, it is necessary to adjust the pH of the aqueous granulating composition with an alkalising agent or a buffering system, to adjust the pH to ≥ 5.5. Ibuprofen granules prepared in this fashion are compressed into a tablet.

Another option is taste masking by inclusion complexation. Cyclodextrins [15-18,129,130] are the most commonly used complexation agents and they mask the taste of bitter drugs by either decreasing its oral solubility on digestion or decreasing the amount of drug particles exposed to the taste buds. Cyclodextrins with lipophilic inner cavities and hydrophilic outer surfaces are capable of interacting with a large variety of molecules to form noncovalent inclusion complexes. The assumption is that only the free drug molecule exhibits a bitter taste, and the extent of taste suppression has been reported to be dependent on the availability of free drug, regardless of the kind and concentration of cyclodextrins.

A well know multi-platform [19,20,131] for taste-masking purposes is Captisol® (CyDex, Inc.), a modified cyclodextrin. This is a polyanionic β-cyclodextrin derivative with a sodium

sulfonate salt separated from the lipophilic cavity by a butyl ether spacer group, or sulfobutylether. Its main advantage is that neutral, cationic and anionic drugs have been effectively complexed by Captisol. It has achieved the taste masking of bitter drugs when incorporated into a solid dosage form, either as a physical mixture or as a complex formed with the drug. The drug complex can be isolated using lyophilisation, spray drying or by application onto another substrate. Tablets made with Captisol can be film-coated using standard formulations and processing techniques because the flow properties are easily controlled by the type of granulation process and the type of milling used.

Chemical modification such as derivatisation has been also applied in some cases. It has been reported that the preparation of ibuprofen derivatives do not have an unpleasant taste and that the anti-inflammatory activity remains the same. In this case, ibuprofen was been converted to ibuprofen p-hydroxyphenylurea ester [132] and it is suitable for oral administration. The improved taste of ibuprofen has also been accomplished by conversion into an aluminium salt [133]. A tasteless form of erythromycin monohydrate has been prepared by chemical modification into erythromycin ethyl succinate. The derivative has been shown to have significantly reduced aqueous solubility.

Ion-exchange resins [134-138,21] are used in drug formulations to stabilise the sensitive components, sustain the release of the drug, disintegrate the tablets and mask taste. Ion-exchange resins are high molecular weight polymers with cationic and anionic functional groups. The drug can be bound to the resin via an oppositely charged resin substrate, forming insoluble adsorbates or resonates through weak ionic bonding so that dissociation of the drug–resin complex does not occur under the salivary pH conditions. In this way, strong taste-masking properties can be achieved to minimise the unpleasant taste and odour of drugs. The resins' properties and the ionic environment of the gastrointestinal tract determine the drug release properties, which involves ion exchange between those in the gastrointestinal tract and those of the drug attached to the resins. The free drug then diffuses into the gastrointestinal tract and the resin passes through without being absorbed. There are several ion exchange resin grades, such as strong and weak acid cation-exchange resins or strong and weak base anion-exchange resins. Strong acid cation resins act through the entire pH range, and weak acid cation-exchange resins function at pH values > 6.0; both can be used for masking the taste of basic drugs. On the contrary, strong base anion-exchange resins act through the entire pH range and can be used for masking the taste of acidic drugs, and the weak base anion-exchange resins function well below pH 7.0 [22]. Polystyrene matrix cation-exchange resins (Indion 204, Indion 234) have been reported to mask the bitter taste of norfloxacin, ofloxacin, ciprofloxacin and chloroquin phosphate [23]; Amberlite IRP-69 is a strongly acidic, sodium form cation-exchange resin used to mask the bitter taste of buflomedil [139]. Resins have also been found to be applicable to consumable solid films [140], where bitter drug agents are adsorbed to the ion-exchange resin. An example of this application is the production of a uniform gel cast on a substrate, followed by drying of the cast to provide a solid film with negligible water content.

5. Solid dispersions

Solid dispersion is a process whereby the drug is distributed or dispersed throughout a dispersion medium. The medium is normally molten or a polymer solution. The granules containing the drug can be formed either by solidifying the molten mixture or evaporating the solvent. There are several approaches for solid dispersion.

Spray congealing [24,25,141] is a method that is generally used for changing the structure of materials to obtain free-flowing powders from liquids and to provide masked pellets ranging in size from ~ 0.25 to 2.0 mm. In this process, the drug substance is allowed to melt, disperse or dissolve in a hot melt of other additives. It is then sprayed into an air chamber where the temperature is below the melting point of the formulation components, to provide spherical congealed pellets. It uses waxes (beeswax) and water-insoluble polymers (ethylcellulose). The particles are held together by solid bonds formed from the congealed melts. Due to the absence of solvent evaporation in most spray congealing processes, the particles are generally non-porous and strong, and remain intact upon agitation. The characteristics of the final congealed product depend in part on the properties of the additives used. The conversion of molten feed into powder is a single, continuous step. Proper atomisation and a controlled cooling rate are critical to obtain a high surface area, and uniform and homogeneous congealed pellets. The main disadvantage of spray congealing is the continuous temperature exposure during processing. Furthermore, the formulations can exhibit sustained release profiles after they have been disintegrated, and coated particles may posses a gritty mouth feel due to the water-insoluble polymers; thus leaving the coated particles intact in the mouth after all the other excipients have disintegrated and dissolved.

Melt granulation [142,143] is another frequently referred to taste masking method using highly water-soluble sugars. For example, this process is involved in the dispersion of sildenafil citrate in a molten mixture containing highly water-soluble sugars (mannitol and xylitol). The mixture is heated above the eutectic temperature (190 – 195 °C) and then is rapidly cooled to form a glassy solid. Optionally, the use of liquid solvents (e.g., methanol, ethanol, polyethylene glycol) facilitates lower melting temperatures. The solvents are removed upon cooling and solidification. Using this approach, a mucoadhesive masked film has been produced in a solid dispersion that dissolves in < 200 s. This approach is less effective for heat-sensitive active agents. Where these are used, it is preferable to use a low melting point solid material as a binder. A low melting point polymer can be melted and used

as a liquid binder to aggregate the powdered active material and excipients into granules. The binder is thereby permanently incorporated into the granules when those granules are cool. By this means, the partial melt granulation of D-pseudoephedrine HCl has been performed using PEG 8000, colloidal silicon dioxide and magnesium stearate by heating up to 72 °C. However, the heat necessary to soften or melt the binder is generally supplied by a high shear mixing device; and thus, the generated heat distribution is difficult to control, which may result in heat inactivation of some active materials. Moreover, the taste masking is incomplete and the addition of taste-modifying agents or further coating is required.

A well-known, solvent-free approach is the hot melt extrusion generally accepted as a method to enhance the dissolution characteristics of poorly soluble drugs [144-146,26]. The melt extrusion process in taste masking is performed by mixing the drug with an extrudable material (e.g., Eudragit E and polyvinylpyrollidone vinyl acetate), with the option of adding a plasticiser. The produced solid dispersion presents a fine, taste-masked powder, achieved, the drug–polymer interactions. These interactions are explained through hydrogen bonding bridges between drug–polymer functional groups. Thus, melt extrusion is especially useful for anionic or cationic (also salt forms) active ingredients. Melt extrusion has been used to reduce the unpleasant taste of ibuprofen and verapamil HCl [202] extruded with Eudragit L100 – 55 and E100. The resulting dispersions have demonstrated high drug loading and increased dissolution rates. In the case of verapamil HCl, the drug–polymer interactions have been confirmed using X-ray photoelectron spectroscopy and differential scanning calorimetry. The first technique has shown interactions between the Cl^- anion and the carboxylic groups of the methacrylate polymer, and the latter has demonstated decreasing glass transition temperatures with increased polymer amounts. The melt extrusion process is advantageous compared with the use of molten materials because of the controllable heat distribution, high mixing efficiency, cost effectivity, continuous processing and scale-up efficiency from a small-scale laboratory extruder to a large scale, production-sized melt extruder. The addition of a plasticiser such as stearic acid or triethyl citrate makes hot melt extrusion effective for heat-sensitive drugs, as extrusion temperatures can be < 50 °C. In some cases, the active agent itself can act as a plasticiser. Ultimately, hot melt extrudates result in the confinement of uncontrollable drug-polymer interactions during storage that could possibly eliminate the taste masking and affect the stability of the active.

Another method of forming the desired taste-masked solid dispersion is precipitation [147,148] followed by solvent evaporation and drying. This is a method of preparing stable dispersions of poorly soluble active agents in the presence of one or more surface stabilisers free of any trace toxic solvents.

This is a straightforward method that consists of, for example: i) dissolving the poorly water soluble active agent in a suitable solvent; ii) adding the formulation from step i) to a solution composed of at least one surface stabiliser to form a solution; and iii) precipitating the formulation from step ii) using an appropriate non-solvent. Using the precipitation process, the active substance is entrapped within the polymer matrix by *in situ* complexation, which eliminates the bitter taste and provides a good mouth feel. The method can be followed by removal of any formed salt, if present, by dialysis or filtration and concentration of the dispersion by conventional means. The resultant nano- or microparticulate active agent dispersion can be formulated into a powder followed by dosage formulation. In this way, cefuroxime axetil and clarithromycin solid dispersions have been prepared by dissolving the bitter active ingredient, a methacrylic acid copolymer and a phthalate polymer in a solvent system, and then recovering the matrix including the active ingredient and the two polymers from the solution. The obtained granules are further coated to yield a non-bitter formulation. Although precipitation can be applied for several active substances, in some cases, either the requirement for a harmful solvent or the stability of the active agents in the solvent are disadvantages. Additionally, increased polymer–drug ratios are necessary to mask the bitter taste, resulting in a slow drug release profile.

6. Conclusions

In this review, the authors have provided a comprehensive description of the taste masking technologies applied in pharmaceutical technologies. It is evident that the taste masking of bitter drugs has received much attention, and enormous amounts of research are underway with the aim of improving drug palatability. There are numerous effective technologies and approaches, varying from common granulation or coating processes to novel fast-disintegrating technologies. The applicability of all these approaches is subject to a drug's properties and depends on the type of dosage form required. Despite the fact that each of the aforementioned conventional techniques presents several advantages, there are some drawbacks. The last decade has seen the introduction of several unique platforms. As a consequence, a wide spectrum of robust formulations are commercially available.

7. Expert opinion

In the last decade, there has been an enormous drive in the development of taste-masking technologies. Several technologies have been developed to improve the palatability of commercial pharmaceutical products, and each depends on the drug's nature and physicochemical properties.

Although the fluidised bed coating method is a well-established process, it cannot always achieve sufficient taste masking of bitter drugs, especially for moisture-sensitive drugs. The novel approach of using molten materials in a solvent-free coating process (Gattecoat) is a successful alternative for effective taste masking without producing drug–polymer interactions.

This approach would also be particularly useful for moisture-sensitive active agents that could not be coated by conventional aqueous-based film coating approaches. The spray congealing, melt-granulation and melt-extrusion techniques are essentially similar to each other, as they all involve melting hydrophobic (waxes) or hydrophilic material (sweeteners; e.g., xylitol, mannitol) and mixing them with the drug, with the molten mixture then being allowed to solidify. With these approaches it is essential to establish the chemical compatibility of the drug and excipients. The first two approaches may be useful for drug substances that are not particularly bitter and are unsuitable for wet granulation, due to the moisture sensitivity of the drug. The hot melt extrusion method is the most attractive due to its ability to create solid dispersions or solid solutions, with effective taste masking once drug–excipient compatibility is proven. This provides improved dissolution behaviour, leading to enhanced bioavailability. Furthermore, the combination of various polymers, the absence of solvents and the efficient scale up makes hot melt extrusion an advantageous process.

Presently, two platform technologies: the fast dissolving dosage forms and the chewable tablets, are dominating the taste masking strategies. In our opinion, the ODT platforms comprise the most advanced taste-masking approaches. Although chewable tablets have been on the market for some time, they are not as effective as the new ODTs. Patients for whom chewing is difficult or painful can use ODT tablets easily. The main advantage of ODT tablets is the unique characteristic of being able to apply several of the aforementioned methods, such as microencapsulation, complexation with ion exchange resins, spray coating or effervescence in some cases, and, thus, they are not limited by the physicochemical properties of the active substance. The outcome is improved patient compliance both in adolescent and elderly populations, decreased onset time, absorption modification and increased bioavailability. In addition, their outstanding pharmacokinetics profiles could expand ODTs into various therapeutic areas where compliance is critical. Nevertheless, there are additional steps to be taken before ODTs are established as the primary taste masking platform.

Bibliography

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. HABIBH W, KHANKARIK R, HONTZ J: Fast-dissolve drug delivery system. *Crit. Rev. Ther. Drug Carrier Syst.* (2000) **17**:61-72.

•• **Very interesting review about ODTs.**

2. LOYD A: Flavors and flavoring. *Int. J. Pharm. Compounding* (1997) **1**:90-92.
3. SEAGER H: Drug-deliver Products and the zydis fast-dissolving dosage form. *J. Pharm. Pharmacol.* (1998) **50**:375-382.
4. CHANG RK, GUO X, BURNSIDE B, COUCH R: Fast-dissolving tablets, *Pharm. Technol.* (2000) **24**:52-58.
5. PROULX SM, MELCHIORREM HA: New dosage forms lead to confusion. *US Pharm.* (2001) **26**:68-70.
6. SMITH AJ, MORAN J, DANGLER LV, LEIGHT RS, ADDY M: The efficacy of an anti-gingivitis chewing gum. *J. Clin. Periodontol.* (1996) **23**:19-21.
7. HYRUP B, ANDRESEN C, ANDREASEN LV, TANDRUP B, CHRISTENSEN T: The MediChew® technology platform. *Expert Opin. Drug. Deliv.* (2005) **2**:927-933.

•• **An excellent review article about chewing gum technologies.**

8. KAWASHIMA Y, NIWA T, HANDA T, TAKEUSHI H, IWAMOTO T, ITOH K: Preparation of controlled-released microspheres of ibuprofen with acrylic polymers by a novel quasiemulsion solvent diffusion method. *J. Pharm. Sci.* (1989A) **78**:68-72.
9. KAWASHIMA Y, NIWA T, HANDA T, TAKEUSHI H, IWAMOTO T, ITOH K: Preparation of prolonged-released spherical micromatrix of ibuprofen with acrylic polymer by the emulsion-solvent diffusion method for improving bioavailability. *Chem. Pharm. Bull.* (1989B) **37**:425-429.
10. SJOQVISTS R, GRAFFEER C, EKMAN J: *In vitro* validation of the release rate and paratability of remoxipride-modified release suspension. *Pharm. Res.* (1993) **10**:1020-1030.
11. GOUIN S: Microencapsulation: industrial appraisal of existing technologies and trends. *Trends Food Sci. Technol.* (2004) **15**:330-347.
12. NII T, ISHII F: Encapsulation efficiency of water-soluble and insoluble drugs in liposomes prepared by the microencapsulation vesicle method. *Int. J. Pharm.* (2005) **298**:198-205.
13. YAN G, FU-DE, YING G, LEI Y, YONG-SHENGY W, LI-NA Z: Preparation of roxithromycin-polymeric microspheres by the emulsion solvent diffusion method for taste masking: *Int. J. Pharm.* (2006) **318**:62-69.

•• **Very interesting article about taste masking using microencapsulation processes.**

14. QI S, DEUTSCH D, CRAIQ DQ: An investigation into the interaction between taste masking fatty acid microspheres and alkaline buffer using thermal and spectroscopic analysis. *Pharm. Sci.* (2006) **95**:1022-1028.
15. FUNASAKI N, KAWAGUCHI R, HADA S, NEYAN S: Ultraviolet spectroscopicestimation of microenvironments and bitter tastes of oxyphenonium bromide in cyclodextrin solutions. *J. Pharm. Sci.* (1999) **88**:759-762.
16. CHALLA R, AHUJA A, ALI J, KHAR RK: Cyclodextrins in drug delivery: an updated review. *AAPS Pharm. Sci. Tech.* (2005) **6**:E329-E357.

• **Interesting review article about the use of cyclodextrins.**

17. SZEJTLI J: *Cyclodextrin Technology.* Kluwer Academic Publishers: Dordrecht, The Netherlands (1988): Chapters 3 and 7.
18. FRÖMMING K.H, SZEJTLI J: *Cyclodextrin in Pharmacy.* Kluwer Academic Publishers: Dordrecht, The Netherlands (1994): Chapters 1 and 4-8.
19. FUNASAKI N, UEMURA Y, HADA S, NEYA S: Reduction of the bitter taste intensity of propantheline bromide by cyclodextrins as predicted by surface

tension measurements. *J. Phys. Chem.* (1996) **100**:16298-16301.

20. FUNASAKI N, KAWAGUCHI R, ISHIKAWA S, HADA S, NEYA S, KATSU T: Quantitative estimation of the bitter taste intensity of oxyphenonium bromide reduced by cyclodextrins from electromotive force measurements. *Anal. Chem*. (1999) **71**:1733-1736.
21. ANON: Taste masking β-lactam antibiotics with macroreticular resins. *Res. Discl.* (1978) **176**:12-13.
22. NANDA A, KANDAPARU R, GARG S: An update on taste masking technologies for oral pharmaceuticals. *Indian J. Pharm. Sci.* (2002) **64**(1):10-17.
- **Interesting article about taste masking technologies.**
23. MANEK SP, KAMAT VS: Evaluation of Indion CRP-244 and CRP-254 as sustained release and taste masking agents. *Indian J. Pharm. Sci.* (1981) **43**:209-212.
24. YAJIMA T, ITAI S, TAKEUCHI H, KAWASHIMA Y: Optimum heat treatment conditions for masking the bitterness of the clarithromycin wax matrix. *Chem. Pharm. Bull.* (2003) **51**(11):1223-1226.
- **Interesting article about taste masking using the spray congealing technology.**
25. YAJIMA T, UMEKI N, ITAI S: Optimum spray congealing conditions for masking the bitter taste of clarithromycin in wax matrix. *Chem. Pharm. Bull.* (1999) **47**(2):220-225.
26. MCGINITY JW, ZHANG F, REPKA M, KOLENG JJ: Hot-melt extrusion process as a pharmaceutical process. *Am. Pharmaceut. Rev.* (2001) **4**:25-36.
- •• **An excellent review article about hot melt extrusion technology and its applications.**

Patents

101. JOHN WYETH & BROTHER LIMITED: US4371516 (1983).
- •• **Very interesting patent describing a novel preparation method of FDDF tablets.**

102. R.P. SCHERER CORPORATION: US5631023 (1997).
103. R.P. SCHERER CORPORATION: US5738875 (1998).
104. CIMA LABS INC.: US5178878 (1993).
- **Interesting patent about FDDF technology using effervescent approaches.**

105. CIMA LABS INC.: US6024981 (2000).
106. CIMA LABS INC.: US5223264 (1993).
107. CIMA LABS INC.: US5607697 (1997).
- •• **Very interesting patent describing an alternative method of FDDF tablets with commercial applications.**

108. CIMA LABS INC.: US6024981 (2000).
109. R.P. SCHERER CORPORATION: US6156339 (2000).
110. LABORATOIRES PROGRAPHARM: US5464632 (1995).
111. YAMANOUCHI PHARMACEUTICAL CO. LTD: US5576014 (1996).
112. ANTARES PHARMA IPL AG: US6696085 (2004).
113. FERTIN FARMA AS: WO200213781 (2002).
114. CIMA LABS INC.: US6221392 (2001).
- **Interesting patent about common fluidized bed approaches on taste masking.**

115. CIMA LABS INC.: WO2002096392 (2002).
116. PFIZER PHARMA: WO9830209 (1998).
117. GATTEFOSSE ETS SA: WO200207706 (2002).
- •• **Very interesting patent about spraying process and use of lipidic substances in taste masking applications.**

118. DAIICHI PHARMACEUTICALS LTD.: US6217910 (2001).
119. ELAN COORPORATION PLC.: US6153220 (2000).
120. EURAND AMERICA INC.: US5814332 (1998).
- **Very interesting patent about spraying process and use of lipidic substances in taste masking applications.**

121. EURAND AMERICA INC.: US5709886 (1998).
122. EURAND AMERICA INC.: US6139865 (2000).
123. NECTAR THERAPEUTICS UK LTD.: US7115280 (2006).
- **Interesting patent describing the application of supercritical fluids.**

124. CENTRE DE MICROENCAPSULATION: US6087003 (2000).
125. THE ROLAND T, DODGE COMPANY: US5393533 (1995).
126. THE ROLAND T, DODGE COMPANY: US5288504 (1994).
127. PHOQUS PHARMACEUTICAL LTD.: WO2004017976 (2004).
128. BRISTOL MYERS SQUIBB: US4916161 (1990).
129. STROPPOLO F, CICCARELLO F, MILANI R, BELLORINI L: WO 2002/41920 (2002).
130. UENO M: JP0411865 (1992).
131. CYDEX INC.: US6046177 (2000).
132. THE UPJOHN COMPANY: US4049700 (1997).
- **Interesting patent about drug chemical modification for taste masking purposes.**

133. UPJOHN MANUFACTURING COMPANY: US4361580 (1982).
134. ASTRUC J, SAMBOT A: GB1180233 (1970).
135. BORODKIN S, SUNDBERG DP: US3594470 (1971).
136. AMERICAN CYANAMID CO.: GB2055575 (1981).
137. ROUSSEL UCLAF: EP27768 (1981).
138. GLAXO GROUP RESEARCH LTD: US5219563 (1990).
139. ABBOTT LAB: EP0501763 (1992).
140. WARNER LAMBERT COMPANY LLC.: US7067116 (2006).
141. KV PHARMACEUTICAL COMPANY: US5494681 (1996).
142. MCNEIL-PPC INC.: US5429825 (1995).
- **Interesting patent about melt granulation approaches.**

143. LAVIPHARM LAB INC.: WO200205820 (2002).
144. ETHYPHARM INC.: US6649186 (2003).
145. ETHYPHARM INC.: US6488961 (2002).
146. ETHYPHARM INC.: US6071539 (2000).
147. UNIVERSITY OF IOWA RESEARCH FOUNDATION: US6372259 (2002).
148. RANBAXY LABORATORIES LTD.: US6565877 (2003).

Websites

201. http://www.cardinal.com/pts/content/aboutus/whoweare/abourbro.asp Oral Technologies: Overview, Cardinal Health, Inc.
202. http://www.rohacell.com/en/pharmapolymers-2.html Taste-Masking via Melt Extrusion Advantages (2004).
- **Interesting internet site about hot melt extrusion applications on taste masking with several examples.**

Affiliation

Dionysios Douroumis BSc, PhD
Senior Scientist, Phoqus Pharmaceutical Limited,
10 Kings Hill Avenue,
Kings Hill, West Malling,
ME19 4PQ, Kent, UK
Tel: +44 0 1732 870227;
FX: +44 0 1732 870228;
E-mail: dionysios.douroumis@phoqus.com